PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PRD 10271-PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/50890	25.11.2003	29.11.2002
International Patent Classification (IPC) or both national classification and IPC		
A61K9/00		
Applicant		
JANSSEN PHARMACEUTICA N.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01.06.2004	05.01.2005
Name and mailing address of the international preliminary examining authority:	Authorized Officer
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/50890

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-126 as originally filed

Claims, Numbers

1-20 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	14
	No:	Claims	1-13,15-20
Inventive step (IS)	Yes:	Claims	14
	No:	Claims	1-13,15-20
Industrial applicability (IA)	Yes:	Claims	1-20
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION V

1. References

D1: US-A-4 596 705 (SCHEPKY GOTTFRIED ET AL) 24 June 1986 (1986-06-24)

D2: WO 95/20384 A (ABBOTT LAB) 3 August 1995 (1995-08-03)

D3: WO 95/07696 A (ABBOTT LAB) 23 March 1995 (1995-03-23)

D4: US 2001/049366 A1 (SINGH ONKAR N ET AL) 6 December 2001 (2001-12-06)

D5: WO 95/23594 A (GERGELY GERHARD ;GERGELY IRMGARD (AT); GERGELY STEFAN (AT); GERGEL) 8 September 1995 (1995-09-08)

D6: WO 01/23362 A (BREITENBACH JOERG ;HANTKE THOMAS (DE); KNOLL AG (DE); REHBOCK BETT) 5 April 2001 (2001-04-05)

D7: WO 97/02017 A (ELAN CORP PLC ;CLANCY MAURICE JOSEPH ANTHONY (IE); CUMMING KENNETH) 23 January 1997 (1997-01-23)

D8: WO 01/30319 A (GORE ASHOK Y ;JOSHI RAJASHREE (US); SUPERGEN INC (US); RUBINFELD J) 3 May 2001 (2001-05-03)

D9: PEETERS, J. ET AL: "Development of an extended release oral dosage form using experimental design" PROCEEDINGS - 28TH INTERNATIONAL SYMPOSIUM ON CONTROLLED RELEASE OF BIOACTIVE MATERIALS AND 4TH CONSUMER & DIVERSIFIED PRODUCTS CONFERENCE, SAN DIEGO, CA, UNITED STATES, JUNE 23-27, 2001 (2001), VOLUME 1, 704-705 PUBLISHER: CONTROLLED RELEASE SOCIETY, 23 June 2001 (2001-06-23), XP001152635

D10: WO 01/22938 A (VERRECK GEERT ;BAERT LIEVEN (BE); JANSSEN PHARMACEUTICA NV (BE)) 5 April 2001 (2001-04-05)

3. **Novelty (Art. 33(2) PCT) - Inventive step (Art. 33(3) PCT)**

a) Pharmaceutical compositions comprising a basic drug compound, a surfactant and a physiologically tolerable water-soluble acid characterized in that the acid:drug compound ratio is at least 1:1 by weight are already known from D1-5.

D1 discloses capsules comprising 250 mg mopidamol, 250 mg fumaric acid and cremophor RH 40 (cf. ex. 14). D1 further discloses hard gelatine capsules filled with pellets comprising 200 mg mopidamol, 105 mg fumaric acid, 150 mg citric acid, polyoxyethylene-hydrogenated castor oil and hydroxypropyl methyl-cellulose (cf. ex. 18). Mopidamol is a basic drug compound. The compositions of D1 have an improved bioavailability.

D2 discloses various solutions comprising a drug compound in the form of a free base, citric acid and cremophor EL, wherein the acid:drug compound ratio is greater

than 1:1 (cf. ex. 10, 11, 14). The compositions provide an improved oral bioavailability for inhibitors of HIV protease.

D3 discloses various soft elastic capsules comprising a drug compound in the form of a free base, citric acid and cremophor EL, wherein the acid:drug compound ratio is greater than 1:1 (cf. ex. 20, 29). The compositions provide an improved oral bioavailability. The compositions provide an improved oral bioavailability for inhibitors of HIV protease.

D4 discloses solution formulations intended for topical application to the eye, ear, nose or skin comprising ciprofloxacin HCl, dexamethasone, boric acid and acetic acid or citric acid, vitamin E TPGS, HCl and/or NaOH, (possibly HEC) wherein the acid:drug compound ratio is greater than 1:1 (cf. table 1-3).

D5 discloses a granular product or tablet containing an effervescent system, which comprises 0,4-4,5% by weight of cisapride, PVP, a tensid and 30-55% of an organic acid, preferably citric acid (cf. claim 12).

The subject-matter of claim 1 thus is not new (art. 33(2) PCT).

Claims 2-13 and 15-20 do not seem to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step.

b) The subject-matter of claim 14 is new since none of the documents discloses or anticipates the specific compositions defined in claim 14 (art. 33(2) PCT).

D6 discloses controlled release, high bioavailability formulations of N-heterocyclic drugs such as those enumerated in claim 14, comprising particles of active agent dispersion in N-vinylpyrrolidone polymer matrix. The polymer matrix increases the bioavailability of the sparingly water-soluble active agents. The compositions may comprise a surfactant and citric acid (cf. claims 3, 6, 13).

The compositions of claim 14 differ from D6 in the proportions of ingredients (cf. claim 1).

The problem to be solved thus is to provide an alternative composition comprising a drug as defined in claim 14 and having an improved bioavailability.

For the man skilled in the art, it is not derivable from D6 nor from any of the other cited documents that the compositions with the specific ratios defined in claim 14 (cf. claim 1) might solve the aforementioned problem.

The claimed effect has been substantiated with one representative compound cited in claim 14 (R278474, composition 10).

The subject-matter of claim 14 may therefore involve an inventive step (art. 33(3) PCT).